TRANSPLANTATION

BENEFITs of belatacept: kidney transplantation moves forward

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New data from the BENEFIT study demonstrate that belatacept improves long-term allograft and patient survival after kidney transplantation, despite higher rates of biopsy-proven acute rejection than with ciclosporin. The noninferiority design of BENEFIT represents a feasible strategy to further the development of innovator drugs to reduce late graft loss.

Refers to: Vincenti, F. *et al*. Belatacept and long-term outcomes in kidney transplantation. *N. Engl. J. Med.* **374**, 333–343 (2016).

In January 2016 history was made in the field of transplantation — Vincenti *et al*. demonstrated that belatacept improves long-term outcomes in kidney transplant recipients[1]. Belatacept is the first new immunosuppressive compound that has been shown

in a phase III trial to improve patient and graft survival since ciclosporin was approved for the prevention of kidney transplant rejection in 1983.

In their follow-up analysis of the BENEFIT study, Vincenti *et al*. found that recipient mortality at 7 years after transplantation was significantly lower with the combination of belatacept plus basiliximab induction, mycophenolate mofetil and glucocorticoids, than with ciclosporin plus the additional agents[1]. The rate of graft failure 7 years after transplantation was also lower among those patients who received the belatacept-based regimen, although this trend did not reach statistical significance.

Short-term renal allograft recipient and graft survival are now excellent, but outcomes are less favourable in the long term. Transplant kidneys fail, and patients die at a constant rate, with only modest improvement since the 1980s[2]. This long-term loss of kidney grafts and patient mortality is explained by a spectrum of pathologies and progressive diseases, including graft rejection, chronic transplant injury, drug nephrotoxicity, cardiovascular disease, infections and cancer.

The wide spectrum of mechanisms of graft loss indicate that it is a misconception to think that targeting one aspect — such as graft rejection or patient mortality — at the expense of others will lead to improved outcomes. For instance, increasing global immunosuppression reduces the risk of acute rejection, but could lead to worse patient outcomes in the long term as a result of an increased risk of infections or cancer. Novel therapies or innovative combination strategies are necessary to achieve powerful immunosuppression whilst avoiding the risks associated with over-immunosuppression.

Almost 5 years ago, in June 2011, the EMA and FDA approved the less-intensive belatacept dosing regimen, based on the results of two phase III trials: BENEFIT[3], which enrolled recipients of standard-criteria-donor kidneys, and BENEFIT-EXT[4], which enrolled recipients of extended-criteria-donor kidneys. Three key reasons exist for enthusiasm about the use of belatacept as a baseline immunosuppressant in kidney transplantation. First, this agent has unique immunosuppressive characteristics. Despite an increased risk of early acute rejection, the long-term data from the BENEFIT study illustrate that belatacept decreases the risk of development of *de novo* donor-specific HLA antibodies in comparison with ciclosporin[1]. Moreover, the prevention of donor-specific antibody (DSA) formation with

belatacept seems to be a dose-dependent effect. Given the great impact of antibody-mediated rejection (ABMR) on kidney graft outcome, and the decreased relevance of reversible T-cell mediated rejection[5], this property of belatacept is a very welcome characteristic with great clinical potential.

Second, in addition to the unique immunosuppressive properties of belatacept, non-immune effects of this agent were noted in the BENEFIT study[6]. Ciclosporin and other currently used immunosuppressants (tacrolimus, sirolimus, and everolimus) are associated with very undesirable metabolic adverse effects, including hypertension, hyperlipidaemia and diabetes mellitus[7]. In BENEFIT, the belatacept-treated patients showed significantly better control of these important cardiovascular risk factors than did the ciclosporin-treated patients [6], which ultimately translated into a numerically decreased risk of death from cardiovascular causes at 7 years (2.7% in the less-intensive and the more-intensive belatacept groups compared with 5.0% in the ciclosporin group)[1], although the number of events was too low to enable robust statistical evaluation.

The third reason for enthusiasm about belatacept is the finding that in the less-intensive treatment group, the percentage of non-cardiovascular deaths was lower than in the ciclosporin group (3.1% versus 6.3%, respectively)[1]. Again, the small number of events does not enable further evaluation of the specific causes of this numerically lower risk. We conclude that the very welcome immunosuppressive characteristics of belatacept do not translate into an increased risk of overall infection-related or cancer-related mortality, at least not in this 7-year time frame. These results were obtained despite enrollment of transplant recipients who were Epstein–Barr virus (EBV)-negative at baseline. EBV-negative patients have an increased risk of developing post-transplant lymphoproliferative disease when treated with belatacept compared with ciclosporin[1], so are currently excluded from the EMA and FDA market authorization of belatacept.

In addition to enthusiasm about belatacept as an immunosuppressive agent in kidney transplantation, the design of the phase III studies used for marketing authorization of this agent[8], and more importantly the long-term follow-up data[1] warrant discussion. Marketing authorization for belatacept was achieved using noninferiority studies for classic end points in kidney transplantation (that is, biopsy-proven acute rejection, graft survival and patient survival) and superiority for measured glomerular filtration rate (GFR). This noninferiority

trial design is in sharp contrast to the design of the phase III studies of all previously approved immunosuppressants in kidney transplantation, which used superiority in patient and graft survival (azathioprine and ciclosporin), or more recently in the rate of biopsy-proven acute rejection without survival improvement (Table 1). Belatacept was thus approved despite a 17% incidence of biopsy-proven acute rejection at 1 year in the less-intense belatacept group, compared to a 7% incidence in the ciclosporin group[3].

In hindsight, the radically different study design, and the definition of the noninferiority margin for biopsy-proven acute rejection (a 20% higher incidence of acute rejection with belatacept compared to ciclosporin was considered noninferior) [8] were crucial for the approval of belatacept. The new data by Vincenti and colleagues show that the increased risk of acute rejection with belatacept compared to ciclosporin did not translate into worse long-term graft outcomes[1]. On the contrary, the ciclosporin group had the lowest risk of unspecified acute rejection but experienced the worst long-term outcomes.

The uncoupling of unspecified acute rejection from the risk of graft failure in the BENEFIT study is unique in the history of novel drugs approved for kidney transplantation, and illustrates that unspecified acute rejection should no longer be considered the primary end point as it was in the early days of transplantation when acute cellular rejection was the main determinant of graft failure[9]. Based on the long-term BENEFIT data, two interesting alternative surrogate markers for late graft loss can be proposed: GFR at 1 year or GFR evolution, and the development of *de novo* DSAs. In the BENEFIT study, however, a lower risk of donor-specific HLA antibody formation and improved graft function with belatacept than with ciclosporin did not translate into a significantly lower risk of death-censored graft failure at 7 years of follow-up[1]. Validation of these potential markers is, therefore, still required.

Despite the repeated efforts of the kidney transplant community to achieve endorsement of surrogate markers for conditional (EMA) or accelerated (FDA) drug approval, no individual or composite marker has been sufficiently validated in kidney transplant recipients who are not at increased risk of graft failure. Moreover, rapid validation of surrogate end points in low-risk kidney transplant recipients is not anticipated because of the lack of new long-term studies using innovator drugs, heterogeneity in the causes of graft failure, the low risk of

ABMR, and the non-specificity of many suggested markers (including GFR, chronic histological injury, inflammation and proteinuria) for specific disease processes.

Thus the question that emerges is whether health authorities will allow conditional or accelerated marketing authorization for therapies in low-risk kidney transplant recipients without thorough validation of putative surrogate end points. In the meantime, the design of the BENEFIT study (noninferiority with broad margins for classic end points and superiority for GFR), is the most effective approach to enable new therapies for kidney transplantation, notwithstanding the inherent assumptions and interpretative difficulties that are associated with the use of a noninferiority design[10].

The BENEFIT study[1] represents an optimistic signal to the clinical transplant community, to academia, to the pharmaceutical industry and to patients, that hope still exists for a brighter future after kidney transplantation. The noninferiority design and the virtual abandoning of unspecified acute rejection as primary end point (by choosing large noninferiority margins) show a feasible trajectory to further development of other innovator drugs that aim to improve long-term outcomes.

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Competing interests

The authors declare no competing interests.

Pullquotes:

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Table 1 | Data used for the approval of immunosuppressive drugs in kidney transplantation

Drug	Year of first approval*	Study regimen	Study design(s)	Primary outcome or definition of efficacy failure	Graft survival	Patient survival	Death-censored graft survival	Acute rejection	Graft function
Azathioprine	1968	Azathioprine & high-dose CS	Case series	Graft loss or death	NA	NA	NA	NA	NA
Ciclosporin	1983	Ciclosporin & low-dose CS	Randomized superiority trials	Graft loss or death	↑	↑	↑	↓	↓
Mycophenolate mofetil	1995	Mycophenolate mofetil, ciclosporin & CS ± ATG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	↓	↑
Daclizumab	1997	Daclizumab, ciclosporin & CS ± AZA	Randomized superiority trials	BPAR by 6 months	=	=	=	↓	↑
Tacrolimus	1997	Tacrolimus, azathioprine, CS & ALG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	↓	=
Basiliximab	1998	Basiliximab, ciclosporin & CS	Randomized superiority trials	BPAR by 6 months	=	=	=	↓	=
Sirolimus	1999	Sirolimus, ciclosporin & steroids	Randomized superiority trials	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	↓	↓
Everolimus	2003	Everolimus, ciclosporin & basiliximab ± CS	Randomized equivalence trial	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	=	↓
Belatacept	2011	Belatacept, mycophenolate mofetil, CS & basiliximab	Randomized noninferiority trial	Noninferiority for BPAR, graft loss and death; superiority for GFR	↗‡	↗‡	=	↑	↑

*FDA or EMA approval. ‡No difference at 1 year or 3 years after transplantation, but significant improvement with belatacept versus ciclosporin at 7 year follow-up[1]. ATG and ALG are not included in this table as these therapies are considered to be biologics so are not subject to the same FDA and EMA regulations as the listed drugs. ALG, antilymphocyte globulin; ATG, antithymocyte globulin; BPAR, biopsy-proven acute rejection; CS, glucocorticoids or other corticosteroids; GFR, glomerular filtration rate; NA, not applicable.